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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/620,227	07/20/2000	Moshe Flugelman	24558	3020

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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/620,227	FLUGELMAN, MOSHE	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,19-25 and 51-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,19-25 and 51-55* is/are rejected.

7)☒ Claim(s) *2 and 8-10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/4/06;4/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/4/06 has been entered.

Claims 13-18 and 51-55 are cancelled.

Claims 1-3, 11-12, 19-20, and 51-53 are amended.

Claims 1-12, 19-25, and 51-55 are presently pending and considered.

Notification of Examiner Reassignment

This Application has been reassigned to Examiner Robert M. Kelly, Art Unit 1633. Future correspondence should be so-addressed. The Examiner's information is located at the end of this action, along with that of the SPE of the Art Unit, Dave Nguyen.

Election/Restriction

It is noted that by canceling claims 13-18 and 51-55, all objections and/or rejections of such claims are necessarily mooted, and thus are withdrawn.

Prior Examiner's Art Rejections

The rejections of Claims 1-10, 12, and 52-55 as being anticipated by Pratt, et al., in the prior Official Action of 12/13/05 (page 3, paragraph 3), are withdrawn.

The rejections of Claims 11, 19-25, and 51, as being unpatentable under 35 USC 103(a) over Pratt, et al., in view of Nakamura, et al., in the prior Official Action of 12/13/05 (pages 3-4, paragraph bridging), are withdrawn.

To wit, while the Examiner does not acquiesce to the Argument, the Examiner feels that different rejections, which are applied below, are more appropriate, and more likely to obtain a speedy prosecution.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claim 1 be found allowable, claim 8 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 1 is drawn to any endothelial cell, and Claim 8 limits these endothelial cells to being obtained from a human or animal donor. However, humans are animals, and animals are the only species with endothelial cells. Hence, Claim 8, despite a slight difference in wording, is a substantial duplicate of Claim 1.

Applicant is advised that should claim 19 be found allowable, claim 25 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 19, drawn to a method of making a vascular graft, is limited by claim 25 to being used in bypass surgery. Hence, such intended use fails to further limit the method of Claim 19, and therefore, despite a slight difference in wording, Claim 25 is a substantial duplicate of Claim 19.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12, 19-25, and 51-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 65, 67, 69-76, 79-80, 83-88 of copending Application No. 10/164,219 in view of U.S. Patent 5,131,907 to Williams, and, in apropos claims, further in view of U.S. Patent No. 6,554,857 to Zilla.

Claims 65, 67, 69-76 of 10/164,219 encompass an artificial vascular graft comprising: (a) a synthetic tube, (b) a coating of adhesion matrix on the interior surface, and (c) a plurality of endothelial cells seeded and cultured on the interior surface of the tube, which cells are genetically altered to express or overexpress UP50. Claim 67 requires the tube to be PTFE. Claim 69 requires the adhesion matrix to be fibronectin. Claim 70 requires the cells to also express/overexpress, by genetic alteration, a proliferation growth factor, which in claim 71 is required to be VEGF. Claim 72 requires the endothelial cells to form a confluent monolayer. Claim 74 requires the tube cross-section to be substantially equivalent to a lumen of a vessel to which it may be grafted, which is about 7-700mm in Claim 75. Claim 73 further requires the steps of coating the exterior of the tube with an adhesion matrix, and seeding and culturing a plurality of smooth muscle cells on such surface, which cells are also genetically altered to express/overexpress a proliferation growth factor. Claim 76 requires the each of the cell types to be obtained from a vein.

Claims 88-89 of 10/164,219 roughly track claims 65, but in Claim 88, except the endothelial cells express both VEGF and UP50, and further requires smooth muscle cells to be seeded and cultured on the exterior, and to be genetically altered to express/overexpress UP50. Claim 89 requires smooth muscle cells to also be seeded and cultured on the interior of the tube.

Claims 79-80 and 83-87 of 10/164,219 encompass a method of making a vascular graft, comprising: (i) providing a tube, (ii) coating the interior of the tube with an adhesion matrix, (iii) seeding a plurality of endothelial cells on the interior surface, and (iv) culturing the plurality of endothelial cells, wherein the cells are genetically altered to express/overexpress UP50. Claim 80 further comprises applying a fluidic shear force at the interior surface during the culturing step. Claim 83 requires the adhesion matrix to be fibronectin. Claim 84 requires the endothelial cells to express/overexpress by genetic alteration, a proliferation growth factor, which is VEGF in claim 85. Claim 86 requires the broad claim to further comprise culturing the cells until they form a confluent monolayer. Claim 87 requires the broad claim to further comprise in steps (ii) coating the exterior with an adhesion matrix, (iii) seeding a plurality of smooth muscle cells on the exterior surface, and (iv) culturing the smooth muscle cells, wherein the smooth muscle cells also are genetically altered to express/overexpress a cell adhesion factor and a proliferation growth factor.

Further, it is noted the whole purpose of such grafts in both Applications is for grafting individuals' vascular systems.

Claims 1-12 of the instant Application encompass artificial grafts comprising a tube coated with a plurality of endothelial cells that have been genetically transformed to express/overexpress at least one endothelial cell proliferating growth factor, and at least one

cellular adherence factor. Claim 2 requires a portions of the cells to express/overexpress each of the factors, but no cell is required to express both. Claim 3 limits the tube to, *inter alia*, PTFE. Claims 4-5 roughly tracks claims 74-75 of the instant Application. Claim 6 requires the endothelial cells to be obtained from, *inter alia*, a vein, which in claim 7 may be the recipient, or from a human or animal donor in claim 8. Claim 9 tracks claim 86 of the instant Application. Claim 10 requires the growth factor be, *inter alia*, VEGF. Claim 11 requires the adherence factor to be UP50. Claim 12 requires the cells to further express a marker protein, by genetic alteration.

Claims 19-25 of the instant Application encompass a method of producing an artificial vascular graft, comprising (a) genetically engineering endothelial cells to express/overexpress the same factors as in claim 1, and (b) culturing the cells on the tube until sufficient endothlelialization has taken place. Claim 20 carries out step (a) by transformation populations of the endothelial cells to express one or the other, which populations may be coextensive. Claim 21 states that step (a) precedes (b), and 22 states that (b) precedes (a). Claim 23 requires the cells to be obtained from, *inter alia*, a vein. Claim 24 further comprises subjecting the cells to fluidic sheer. Claim 25 is the intended use in bypass surgery.

The differences between the inventions appears to be that of coating the surfaces of the tube with fibronectin, and the use of smooth muscle cells on the exterior of the tube.

With regard to the use of fibronectin, Williams teaches that cells so-seeded suffer from sheer forces *in vivo*, thereby removing the cells and reducing graft patency (col. 5, paragraph 3). Moreover, because such cells missing from the surface are detrimental to graft patency, the cells are grown a confluent monolayer (Id.).

With regard to the use of smooth muscle cells in the exterior, Zilla teaches that long-term patentcy of such grafts can only be obtained through the establishment of functional neomedia, requiring the presence of smooth muscle cells in the exterior of the graft (col. 2, paragraph 4). Moreover, it is noted that Zilla teaches autologous cells are the most successful (col. 1, paragraph 2) and it is evident from every reference the ultimate objective of these methods is to make grafts.

Hence, at the time of invention, it would have been obvious to modify the methods and compositions of the instant Application with Williams, and where apropos, also Zilla, to arrive at Applicant's invention. The Artisan would have been motivated to do so in order to make grafts with higher patentcy. Moreover, the Artisan would have had a reasonable expectation of success, as each reference had already taught the various advantages, and there is no reason to believe it would not work.

This is a provisional obviousness-type double patenting rejection.

It is noted that this Application has been allowed, although not yet issued, and hence, future rejections may not be provisional, but full-obviousness rejections.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12, 19-25, and 51-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2,5-7,11,and 34-35 of copending Application No. 10/163,387 view of U.S. Patent No. 5,131,907 to Williams, and, in apropos claims, further in view of U.S. Patent No. 6,554,857 to Zilla. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Applicant's claims encompass endothelial cells genetically altered express at least UP50, and further to express one or more cell proliferation growth factors, including VEGF-A, and further to express a selection or reporter marker.

Claims 1-12 of The instant Application encompass artificial grafts comprising a tube coated with a plurality of endothelial cells that have been genetically transformed to express/overexpress at least one endothelial cell proliferating growth factor, and at least one cellular adherence factor. Claim 2 requires a portions of the cells to express/overexpress each of the factors, but no cell is required to express both. Claim 3 limits the tube to, *inter alia*, PTFE. Claims 4-5 roughly tracks claims 74-75 of the instant Application. Claim 6 requires the endothelial cells to be obtained from, *inter alia*, a vein, which in claim 7 may be the recipient, or from a human or animal donor in claim 8. Claim 9 tracks claim 86 of the instant Application.

Claim 10 requires the growth factor be, *inter alia*, VEGF, and the Specification teaches VEGF-A, as VEGF-165 (e.g., p. 47). Claim 11 requires the adherence factor to be UP50. Claim 12 requires the cells to further express a marker protein, by genetic alteration.

Hence, in view of the instant 10/163,387, it would have been obvious to make the endothelial cells of Applicant's claimed invention. The Artisan would have been motivated to do so in order to make the vascular grafts taught in 10/163,387. Moreover, the Artisan would have had a reasonable expectation of success, as 10/163,387 had taught such vascular grafts. Lastly, the methods of making and using are the same in each specification.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim1-12, 19-25, and 51-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of copending Application No. 11/344,870.

Alternatively:

Claims 1-12, 19-25, and 51-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of copending Application No. 11/344,870 in view of Lambert, et al. (1994) Circulation 90(2): 10031011, and Walter, et al. (2004) Circulation, 110: 36-45.

The instant Application is drawn to is drawn to artificial vascular grafts comprising endothelial cells in the lumen, which express/overexpress a growth factor and a cellular adherence factor. Such growth factors include VEGF, and such adherence factors include up50. Other claims are drawn to methods of making such grafts, making the endothelial cells, and a method of replacing/bypassing a portion of the vascular system. The balance of the dependent claims are similar in scope to those of Application No. 11/344,870, or the 11/334,870 Application specifically teaches the aspects (e.g., PTFE containing grafts are taught in the 11/334,870 Application).

The 11/344,870 Application is drawn to implantable devices (of which the specification teaches specifically vascular grafts), which devices comprise an inhibitor of smooth muscle cell proliferation, which may be UP50, and the growth factor may be VEGF. Similarly methods of treating vascular disease are claimed (claims 19), by which the UP50, or inhibitor, inhibits smooth muscle cell proliferation, inhibiting restinosis. It is noted that the structure of these

grafts and the methods of use are the same in each Application: for e.g., bypass surgery. Hence, these claims are provisionally obvious over each other themselves.

However, due to Applicant's method of claiming the invention in the 11/344,870 Application, the door is left open to grafts which contain factors which decrease smooth muscle cell proliferation and contain the growth factor themselves, without the endothelial cells expressing such factors.

Lambert however, teaches the use of inhibitors of smooth muscle cell proliferation, including forskolin (e.g., ABSTRACT). Further, Walter teaches the use of VEGF encoding stents to increase proliferation, while still being able to inhibit restinosis (e.g., ABSTRACT).

Hence, it would have been obvious by the time the 11/334,870 Application was filed (it is noted that such Application has a filing of 7/20/06, and is a CIP in the chain of priority to the instant Application, and the new subject matter appears to be the inhibitors and growth factors in the stent, rather than the cells) to modify the 09/620,227 invention to utilize stents containing plasmids encoding VEGF, and further to contain inhibitors of smooth muscle cell proliferation, as taught by Walter and Lambert. The Artisan would have been motivated to do so in order inhibit restinosis as well as increase smooth muscle proliferation in bypass surgery, as taught by the references. Moreover, the Artisan would have had a reasonable expectation of success, as each of these modifications work, and there is no reason to believe they would not work in combination.

These are provisional obviousness-type double patenting rejection.

Claim Objections

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 2 recites that portions of the endothelial cells of Claim 1 are transformed with the at least one endothelial growth factor and, in a separate, non-coextensive portion, are transformed with the at least one cellular adherence factor. As such, these endothelial cells are not all transformed with at least one endothelial growth factor, and at least one cellular adhesion factor, as required of claim 1. Hence, such claim must be written in a form independent of Claim 1.

Claims 8-9 are objected to because of the following informalities:

Claim 8 recites that the endothelial cells are obtained from humans or any animal donor. The Examiner has found no evidence for endothelial cells which are not animals, and hence, the claim fails to limit the parent claim.

Claim 9 recites "form a confluent monolayer **at** said luminal surface". However, proper English is "form a confluent monolayer **on** said luminal surface".

Claim 10 recites "VEGF, acidic or basic FGF, and HGF". However, such limitation leads to confusion as to whether acidic is a separate molecule. Amending the claim to recite "VEGF, acidic FGF, ~~or~~ basic FGF, and HGF" would be remedial.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 recites "until **sufficient endothelialization** of said luminal surface is achieved". Such sufficient endothelialization is not clear for its metes and bounds, as what is sufficient to one person, may be insufficient to another.

Claims 20-25 are rejected for depending from a rejected base claim without overcoming the lack of clarity in such base claim.

Claim 20 recites the limitation "wherein step (a) is effected by transforming a first portion [to express/overexpress said at least one endothelial growth factor] and genetically transforming a second portion [to express/overexpress said at least one cellular adherence factor]. It is unclear how by transforming only a portion of all the cells with each sequence, expression/overexpression occurs in all the cells.

Claims 6 and 23 each recite that the endothelial cells are derived from bone marrow progenitor or peripherial blood progenitor cells. Such "derived" is so excessively broad as to render the claimed limitations indeterminate. To wit, (i) are cells derived from other sources but in equivalent structure encompassed? Further (ii) derived can mean that the cells were used for their chemical components as food for other cells or be used for their genes in transforming other cells that are used. It would be remedial to amend the claim to include the structure required to

be so-derived, and further make clear whether other endothelial cells are encompassed by such structure as would preclude these endothelial cells.

Claim 24 recites the limitation "used in bypass surgery". Such claim is unclear as it is unclear whether Applicant is claiming a method of bypass surgery, which is improperly dependent, whether Applicant is claiming an intended use, which is not further limiting on compositions, and what aspect of bypass surgery the graft is used in, i.e., "used" is a broad term, and the graft could simply be used to tie off a vessel, or any other use, during bypass surgery.

Claim 51 recites the limitation "concurrently". It is unclear whether this limitation is meant to preclude the sequential transformation of the cells with each sequence encoding a factor, or to preclude the non-concurrent expression of all the heterologously-encoded factors in the cell.

Claim 52 is unclear for its metes and bounds. The claim is drawn to a method of replacing or bypassing at least a portion of a vascular system of an individual, yet, the graft appears to only require fluid connection with the blood of the system. Hence, it is unclear how, with only a single fluid connection can provide for replacement or bypassing a portion of the vascular system.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 19-25, and 51-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 11 encompasses a generic UP50, which necessarily encompasses a series of proteins, from many species (any species with cells that express adherence factors may have such protein). Further, because the UP50 of Claim 11 is further limiting on the "at least one cellular adherence factor", it is clear that all the pending claims encompass this limitation, if not explicitly stating UP50. Applicant's description of the UP50 is limited to the fact that UP50 is DANCE and the protein is found in Genbank Accesssion number AF093118) or (GenBank Accession Number AF112152) and further, Applicant's subsequent disclosure demonstrates that UP50 is a recently discovered protein (Application No. 10/164,219, SPECIFICATION, paragraph 0068). However, the only UP50s known in the Art at the time of invention were those of mouse and human (e.g., Nakamura, et al. (1999) Proc. Natl. Acad. Sci., USA., 274(32); 22476-83). Moreover, the only specific structure known for these proteins is that they contain RGD and EGF-like motifs, like many other vascular extracellular matrix proteins (Id., p. 22476, col. 2, paragraph 3); however, UP50/DANCE appears to contain distinct properties from these other proteins, being involved in developmental arteries and atherosclerotic legions. The structure for such properties was not identified such that the Artisan would be aware of the structure required of a UP50 protein from any species.

Further, given that Applicant has described UP50 as being distinct from DANCE in the present specification (e.g., paragraph 0107), further supported by the fact that Applicant Applicant has amended DANCE to UP50 in order to overcome a rejection, it is clear that Applicant was not in possession of any UP50 except that encoded by nucleotide sequence of GenBank Accesssion number AF093118, and only that sequence which was present as that Accession number at the time of filing of the present Application.

Given the number of species to which this UP50/DANCE may be isolated, and the fact that Applicant's claims encompass any functional portion of UP50, and the fact that so little is known about UP50, the Artisan could not determine Applicant to have been in possession of any UP50, but only those of mouse and human, and only the full-length sequences. This is further supported by Applicant's amendment of Claim 11 from DANCE to UP50 to overcome the Art.

Claim Rejections - 35 USC § 112 - Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 65-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(i) An artificial graft comprising:

(a) a synthetic tubular element comprising a two ends such that the lumen is exposed on each of the tubular element;

(b) a coating of adhesion matrix on the lumen; and

(c) a plurality of cells coating the adhesion matrix,

wherein the endothelial cells are genetically altered to express or over-express one or more cell adhesion factors, and further genetically transformed to express or over-express one or more cell proliferation growth factors, and wherein further the lumen cross-sectional area of the tubular element is substantially equivalent to the lumen cross-sectional area of a blood vessel;

(ii) methods of making the grafts commensurate with the scope of (i);

(iii) a method of producing genetically transformed endothelial cells, the method comprising:

(a) obtaining endothelial cells from a source selected from the group consisting of a segment of a vein and bone marrow progenitor cells;

(b) transforming said endothelial cells with a nucleotide sequence encoding at least one sequence to express and over-express at least one endothelial cell proliferation growth factor, each coding sequence operably linked to a promoter; and

(c) transforming said endothelial cells with a nucleotide sequence encoding at least one sequence to express or over-express at least one cellular adherence factor,

wherein the cells then express both the at least one cellular adherence factor and the at least one endothelial cell proliferation growth factor concurrently;

(iv) A method of replacing or bypassing a portion of a vascular system of an individual, comprising the step of implanting the vascular graft of (i) into the vascular system of the individual by grafting the ends of the tubular element onto the vessel such that one end is grafted

onto the incoming blood supply vessel, and the other is grafted onto the outflowing blood vessel portions, thereby replacing an excised portion, or bypassing a larger portion of the blood vessel,

does not reasonably provide enablement for closed tubular elements, lack of an adhesion matrix coating the lumen, cross-sectional areas of the lumen not being substantially equivalent to that of a blood vessel, only portions of the endothelial cells being genetically altered to express or over-express cell adhesion factors or cell proliferation growth factors, replacement of the whole vascular system, or bypassing/replacing vessels by only connecting one end of the tubular element to the blood supply. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant's claims are broad, encompassing any synthetic tubular element, with any endothelial cells seeded and cultured on the surfaces of the element, without regard to attachment mechanisms, and wherein any portion of the cells express at least one cell adhesion factor, and any other portion of the cells express at least one cell proliferation growth factor, lack of an adhesion matrix for the cells, replacement of the whole vascular system, and bypassing/replacing vessels by simply connecting one end of the vessel to the blood supply, along with methods of making such compositions, and methods of bypassing/replacing with such compositions.

It has long been recognized in the art of artificial grafts that many materials may be used, and that endothelial cells may be seeded onto the interior surface of such grafting materials; however, it is generally recognized that many of these materials, particularly Teflon, require that the surfaces be coated with an adhesion matrix, in order to provide the surface characteristics required for the cells to attach. Such is because the cells do not adhere properly to such surfaces

(U.S. Patent Application No. 2003/0229393 to Kutryk, et al., filed 2/6/03, published 12/11/03, paragraph 0016). Therefore, in order to maintain cells on the surface of such vascular grafts, the surface must first be coated with an adhesion matrix. Applicant's specification does not overcome this aspect, because although stating that such cells may be seeded without matrix (e.g., paragraph 0013), the experiments discussed always use a coating of fibronectin before applying cells to a surface of the graft (e.g., paragraph 0110). Moreover, the specification does not teach any or which surfaces would not require the matrix deposition for cellular attachment. Hence, the Artisan would predict that the absence of matrix would not allow for attachment, and to determine which matrix compositions allow for such attachment, especially considering the *in vivo* use, would be considered extensive, undue experimentation.

With regard to the portions of cells expressing cell adhesion factors and, optionally, cell proliferation growth factors, it is not reasonably predictable that a portion of such cells, and what size portion would be required to produce enough of the factors to produce the requisite adhesion and growth characteristics, because such is a function of the potency of the factor produced, its mechanism of action, and the levels of production of the factor provided by the cell, which is a function of the specific vector and promoter and transcriptional and translational and processing elements encoded. For example, Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA

produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82).

Although Eck is generally directed to *in vivo* gene therapy, the analogous situation is applied. When Eck addresses targeting, that is equivalent to a subpopulation in Applicant's situation, where only a portion of the cells are reached and transformed. When Eck discusses the trafficking, the levels of mRNA produced, the stability of the mRNA, the amount and stability of the protein produced and compartmentalization or secretory fate, such is equivalent to Applicant's specific factor and how it acts. Essentially, this means that the particular factor used is a function of the promoters and other elements used to express the factor and a function of the population which is so-producing the end product. Moreover, this is all influenced by the potency of the end product. A strongly mitogenic growth factor would need to be produced less than a weakly mitogenic growth factor, as less is needed to produce the same effect. Hence, the Artisan could not reasonably predict whether, through use of any particular growth factor encoded, that any particular population size would produce the desired effect. This is all emphasized in the case of the cell adhesion factors. Some factors, like integrins, bind to extracellular matrix proteins, like collagens, (Stryer (1988) Biochemistry, 3rd Ed., by WH Freeman and Co., New York, NY, p. 277), and hence are specific to the subset of cells which express them, but other cell adhesion factors, like collagen, actually form the extracellular matrix to which all the cells may bind (Id.), and therefore, would be specific to the levels of such cell adhesion factor so-produced by the subpopulation of cells expressing the cells and the level of potency for binding of such adhesion factor. Hence, the Artisan would not be able to reasonably

predict in any case whether any particular factor, expressed in any particular subpopulation, would produce enough protein for a long enough time to have an effect, and to determine the particular vectors and expression elements needed to produce such an efficacious effect would cause the Artisan undue experimentation. Moreover, Applicant's specification does not overcome such lack of enablement, because although stating that any particular factors may be used in any subpopulation or subpopulation (e.g., p. 4, paragraph 0014), Applicant's experiments only discuss populations where 100% of the cells are transformed (e.g., paragraph 0110).

With regard to closed circular tubular elements, it would be impossible to seed cells into the lumen, as the tube is closed, and any cells would die from exposure to oxygen, and hence, it is not reasonably predictable such a tubular element could be obtained.

With regard to grafts not equivalent to that of a blood vessel in cross-sectional area, such grafts would not be useful in any grafting, as they could not be grafted onto a vessel, and hence, it is not reasonably predictable that they could form a vascular graft, as is the purpose taught throughout the specification.

With regard to grafting, the art fails to demonstrate the complete replacement of a vascular system with artificial grafts. In fact such is logical in many cases, such as PTFE, as the grafts diffuse oxygen and nutrients too slowly, if at all, to allow for the vessels to deliver the oxygen and nutrients to the animal. Hence, it is not reasonably predictable that such replacement of the vascular system of any animal would not kill the animal before any beneficial effect was seen.

With regard to grafting only end of a graft into the blood supply, the patient would necessarily bleed out, from blood flowing out the other end, and hence, it is not reasonably predictable such a grafting would demonstrate a beneficial effect prior to dying.

Furthermore, the methods of making the graft, and those of using the graft would necessarily be limited to that structure of the claims to the graft.

Hence, the Artisan, given the knowledge in the Art and Applicant's disclosure, would have to perform experimentation to determine which tubular element materials could be used, with or with adhesion matrix, to seed endothelial cells onto, and allow replacement of a whole vascular system, or any beneficial affect of simply applying one end of the tube to the vascular system, and to further determine which combinations of portions cells should express or overexpress which factors, to provide for proper adherence and growth, and allow for the diffusion of sufficient nutrients and gasses to allow for a whole vascular system to be replaced. Such experimentation amounts to undue experimentation, as it amounts to inventing Applicant's claimed subject matter for Applicant.

Therefore, Applicant's claims are subject to the scope of enablement provided in the initial form paragraphs.

Claim Rejections - 35 USC § 103 – Pratt/Williams/Stryer/Schwartz

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10, 12, 19-25, and 51-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,785,965 to Pratt, et al., filed 5/15/96, patented 7/28/98; U.S. Patent No. 5,131,907 to Williams, et al., filed 3/6/91, patented 7/21/92; Stryer (1998) Biochemistry, 3rd Ed., WH Freeman & Co., New York, NY, p. 277; and U.S. Patent No. 5,925,564 to Schwartz, et al., filed 7/7/95, patented 7/20/99.

Pratt teaches vascular grafts, including PTFE grafts, wherein the lumen is seeded with endothelial cells transformed to express VEGF (ABSTRACT, col. 1, paragraph 3-col. 3, paragraph 3). Moreover, Pratt teaches vascular grafts with a cross-section of 7.1 mm-squared (cols. 8-9, paragraph bridging), which is the cross-section size of the vessel which is to grafted (Id.). However, Pratt does not teach such cells co-transformed with a transgene to express or overexpress a cell adhesion protein.

On the other hand, Williams teaches that cells so-seeded, as taught by Pratt, suffer from sheer forces *in vivo*, thereby removing the cells, and reducing graft patency (col. 5, paragraph 3). Moreover, because such cells missing from the surface are detrimental to graft patency, the cells are desireably grown to a confluent monolayer (Id.).

Stryer teaches that one protein that binds cells to the cell matrix is laminin (p. 277, paragraph 3). However, Stryer does not provide a method to produce the laminin in the endothelial cells to decrease the loss of such cells due to sheer forces.

On the other hand, Schwartz discloses expression vector systems for the expression of the laminin transgene (ABSTRACT; col. 9 paragraph 1).

At the time of invention by Applicant, it would have been obvious to make a vascular graft of PTFE that has a lumen coated with fribrinogen and seeded with endothelial cells, as

taught by Pratt, and further that the endothelial cells would be transformed to express laminin, as taught by Schwartz. The Artisan would have been motivated to do so in order to increase the resistance to sheer forces as taught by William through increasing cell attachment to matrix, as taught by Stryer. Moreover, the Artisan would have had a reasonable expectation of success, as Pratt had already made the vascular graft, and Schwartz had already produced the expression system for laminin. Furthermore, these grafts are made by the same procedures. Lastly, because it is unimportant whether the cells are transformed prior to or after forming a monolayer on the tubular element, it would be obvious to transform these cells either prior or after forming such a monolayer. These are simply two well known methods of achieving the same result.

Claim Rejections - 35 USC § 103 – Pratt/Williams/Nakamura

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12, 19-25, and 51-55 are also rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,785,965 to Pratt, et al., filed 5/15/96, patented 7/28/98; U.S. Patent No. 5,131,907 to Williams, et al., filed 3/6/91, patented 7/21/92; and Nakamura, et al. (1999) J. Biol. Chem., 274(32): 22476-83.

Pratt teaches vascular grafts, including PTFE grafts, wherein the lumen is seeded with endothelial cells transformed to express VEGF (ABSTRACT, col. 1, paragraph 3-col. 3, paragraph 3). Moreover, Pratt teaches vascular grafts with a cross-section of 7.1 mm-squared

(cols. 8-9, paragraph bridging), which is the cross-section size of the vessel which is to grafted (Id.). However, Pratt does not teach such cells co-transformed with a transgene to express or overexpress a cell adhesion protein.

On the other hand, Williams teaches that cells so-seeded, as taught by Pratt, suffer from sheer forces *in vivo*, thereby removing the cells, and reducing graft patency (col. 5, paragraph 3). Moreover, because such cells missing from the surface are detrimental to graft patency, the cells are desireably grown to a confluent monolayer (Id.).

Nakamura teaches DANCE (which, as noted in the written description rejection, is UP50), which promotes attachment via interaction with RGD to the extracellular matrix (p. 22477, col. 1, paragraph 1). As demonstrated by Nakamura, this produces greater cell interaction through its binding between surface integrins on other cells (p. 22438, col. 1). Moreover, Nakamura teaches an expression vector for such protein in endothelial cells (Id., col. 2, paragraphs 3-4).

At the time of invention by Applicant, it would have been obvious to make a vascular graft of PTFE that has a lumen coated with fribrinogen and seeded with endothelial cells, as taught by Pratt, and further that the endothelial cells would be transformed to express UP50, as taught by Nakamura. The Artisan would have been motivated to do so in order to increase the resistance to sheer forces as taught by William through increasing cell attachment to matrix. Moreover, the Artisan would have had a reasonable expectation of success, as Pratt had already made the vascular graft, and Nakamura had already produced the expression system for UP50. Furthermore, these grafts are made by the same procedures, as similarly explained above.

Response to Argument – Pratt and Nakamura

Applicant's arguments are in large part mooted by the new rejection of the claims, however, those aspects drawn to the combination of Pratt and Nakamura are addressed in part because they have some relevance to the present rejections.

Applicant's argument of 4/4/06 has been fully considered and not found persuasive.

Applicant argues that Pratt is individually complete in and of itself, and therefore, there is no need to modify Pratt, in fact, such teaches against modification (p. 10).

Such is not persuasive. If Applicant's argument was correct, there would never be an improvement claim, or for that matter, an improvement made, to anything that works.

Applicant argues that Nakamura would render Pratt unsatisfactory for its intended purpose, because Nakamura teaches that UP50 may act as a growth break, thereby stopping the growth of the cells to confluency (pp. 10-11, CoSubmitted Flugelman Declaration of 4/4/04, paragraphs 10-11).

Such is not persuasive. First, Applicant's claims do not require the cells to grow to confluency, and further, the Artisan would readily recognize that transforming the cells after they have grown to confluency would yield same result. Either way, it would be obvious to one of skill in the Art to use UP50 as a cellular adhesion factor.

Applicant argued that vascular grafts are still not extensively used, there is long felt need for improved grafts that resist sheer flow, and the art has not "implemented" the invention, indicates the invention is not obvious (pp. 11-12).

Such is not persuasive. The desire in the provided art is to provide resistance to sheer flow. The Art has made such invention obvious, as made by the rejection, and as such it is properly rejected.

Applicant argues that they have provided an improvement in the art, with post-filing demonstration of improved attachement versus not expressing UP50 (pp. 12-13).

Such improvement was expected, as provided in the Art rejections above.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Robert M. Kelly, Ph.D.
Examiner, USPTO, AU 1633

Patents Hoteling Program
2C55 Remsen Building
(571) 272-0729

Joe Woitach
AU1632